Environmentally Induced Cardiovascular Malformations

The NIEHS invites applications to study environmental agents that cause cardiovascular malformations (CVMs). The purposes of this PA are to stimulate research to characterize environmental agents that cause alterations in the development of the cardiovascular system and thereby lead to CVMs, and to investigate the cellular and molecular mechanisms involved in the development of these CVMs. The use of mammalian and nonmammalian animal models, including transgenic and gene knockout animal models, and of state-of-the-art molecular biology techniques such as genomics and proteomics is encouraged, as well as collaborations between environmental health scientists and developmental biologists, to develop research programs to address the high rate of CVMs.

CVMs are the most common type of birth defect among live births in the United States, occurring in approximately 0.8% of live births. The most common types of CVMs include atrial or ventricular septal defects, transposition of the great vessels, persistent truncus arteriosus, teratology of Fallot, and coarctations. Despite the importance of these in malformations, in terms both of human suffering and cost to the health care system, the causes of most cases of CVMs are not known.

Etiologic factors that have been identified include genetics, maternal diseases such as diabetes, certain drugs such as phenytoin and cocaine, and dietary factors such as folic acid deficiency, vitamin A excess, and copper deficiency. In addition, certain environmental chemicals have been shown to be associated with cardiac malformations. For instance, in one large epidemiologic study of cardiac malformations, the Baltimore–Washington Infant Study, exposure to such environmental factors as paints, solvents, degreasers, and pesticides was associated with increased cardiac malformations.

Epidemiologic studies have also reported CVM associations with air pollutants (ozone and carbon monoxide) and trichloroethylene (TCE). In addition, environmental contaminants such as TCE, bisdiamine, and dioxin have been shown to be cardiac teratogens in animal studies.

Despite the evidence for an environmental role in CVMs, the list of environmental agents tested for teratogenic effects on the heart is limited, and relatively little research has been done on the cellular and molecular basis of the teratogenic effects of environmental agents or on the possible interactions between environmental exposures and other factors such as diet and genetics. Recent advances in genomic and molecular biology technology and in the understanding of the development of the fetal heart make this an opportune time to initiate such studies.

Specific areas of interest to the NIEHS include, but are not limited to, the following: 1) characterization of new potential environmental cardioteratogens that would include the types of CVMs induced, dose–response evaluation, identification of specific windows of vulnerability to the agent, and development of preliminary data for further mechanistic studies; 2) use of forward and reverse mutagenesis studies in model organisms to determine the genes altered by specific cardiovascular developmental toxicants and the relationship of the altered gene activity to dysmorphogenesis; 3) characterization of global gene expression profiles in the developing heart of model organisms associated with the normal range of development and after a developmentally toxic exposure (the relationship between the changes in gene expression and the developmental lesion should be assessed); 4) use of genomic and/or proteomic profiling to determine how well data on toxicant-induced malformations can be extrapolated across species; 5) identification and evaluation of specific signal transduction pathways and the associated genetic regulatory circuits that might be sites of action of developmental cardiovascular toxicants (the causal relationships between exposure and the CVMs should be developed); and 6) determination of the potential for interactions between exposures to environmental agents and genetic susceptibility that increase the risk for cardiovascular developmental toxicity.

This PA will use the NIH R21 and R01 award mechanism(s). Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applications submitted in response to this PA will be accepted at the standard application deadlines, which are indicated in the PHS 398 application kit. Complete information on this PA is available at http://grants.nih.gov/grants/guide/pa-files/PA-02-093.html.

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The Role of Gene–Environment Interactions Underlying the Health Disparity of Premature Birth

The National Institute of Child Health and Human Development (NICHD), the National Institute of Nursing Research (NINR), and the NIEHS are seeking research grant applications on the role of gene–environment interactions underlying the health disparity of premature birth in the United States. The major objective of this PA is to determine the role of gene–environment interactions and genetic diversity in the health disparity of premature birth. This PA specifically addresses the need to better understand how adverse societal, behavioral, and environmental conditions alter gene expression and interact with diverse genetic backgrounds to increase a woman's susceptibility for premature birth in high-risk racial and ethnic groups in the United States. Furthermore, the PA addresses the need for the identification and functional characterization of genetic markers that increase the risk of premature birth among these high-risk populations. Multidisciplinary applications linking biomedical scientists with social and behavioral scientists are highly encouraged.

This PA seeks research projects focused on one or more of the following goals:

1) Determine changes in gene or protein expression under adverse societal, behavioral, or environmental conditions to identify candidate genes or their corresponding proteins that may be involved in increasing a woman's susceptibility for premature delivery in high-risk racial and ethnic populations in the United States. Examples include, but are not limited to, studies utilizing gene or protein expression profiling by high-throughput platforms, such as DNA arrays, protein arrays, and protein capture/SELDI-TOF mass spectrometry.

2) Determine the functional relevance of an identified gene or protein for increasing a woman's susceptibility for premature delivery under adverse societal, behavioral, or environmental conditions in high-risk racial and ethnic populations in the United States. Examples include, but are not limited to, studies elucidating the function or mechanism of action of an identified gene or protein in precipitating premature delivery.

3) Determine genomic differences that serve as potential candidate markers for increasing a woman's susceptibility for premature delivery under adverse societal, behavioral, or environmental conditions in high-risk racial and ethnic populations in the United States. Examples include, but are not limited to, linkage studies using high-throughput genotyping platforms to uncover genomic differences, such as sequence repeats and multiple or single nucleotide polymorphisms.

4) Determine the functional relevance of candidate genomic markers associated with an increased risk for premature birth in high-risk racial and ethnic populations in the United States. Examples include, but are not limited to, studies that determine the functional consequence of these markers as it relates to gene expression, function, or regulation.

Applicants are encouraged to consider the complexity of issues surrounding the meaning and assessment of race and ethnicity, because an individual's identification with a particular racial or ethnic group may involve not only an individual's genetic background but also his or her cultural and geographical identity. As appropriate for their particular proposals, applicants should consider the degree of genomic heterogeneity within racial and ethnic populations and that genetic differences may not apply broadly to a specific race or ethnic group, and should consider the new Office of Management and Budget (OMB) directives on classifying race and ethnicity. NIH policy on reporting race and ethnicity data based on OMB directives is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

Because the NIEHS has expanded its research agenda through the Environmental Genome Project, the NIEHS is particularly interested in applications that examine the complex interplay of genes and the environment. The understanding of the critical role of genetic susceptibility and sensitivity to environmental exposures will lead to more effective disease prevention and improved public health.

This PA will use the NIH research project grant (R01) award mechanism. Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applications submitted in response to this PA will be accepted at the standard application deadlines indicated in the PHS 398 application kit. Complete information on this PA is available at http://grants.nih.gov/grants/guide/pa-files/PA-02-102.html.

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Centers for Population Health and Health Disparities

The purpose of the Centers for Population Health and Health Disparities (CPHHD) is to support interdisciplinary research leading to an understanding and reduction of health disparities in domestic populations. Applicants are invited to propose multilevel, integrated research projects that will elucidate the complex interactions of the social and physical environment, mediating behavioral factors, and biologic pathways that determine health and disease. The CPHHD is expected to create an environment conducive to interdisciplinary and reciprocally beneficial collaborations among biomedical scientists, social scientists, and affected communities, with the common goal of improving population health and reducing health disparities.

This is a trans-NIH request for applications (RFA) sponsored jointly by the NIEHS, the National Cancer Institute (NCI), the National Institute on Aging (NIA), and the Office of Behavioral and Social Science Research. Applicants are encouraged to propose research across disease outcomes or health-related issues relevant for these institutes.

To achieve this goal, the CPHHD will support three or more thematically linked research projects, facility cores that support two or more projects, an administrative core, and pilot projects. The CPHHD will present opportunities to concurrently study biological, behavioral, psychological, cultural, and social precursors of disease.

A key objective is to generate a research program that embraces the concept of multiple levels of analysis in health sciences to examine factors operating at the social/environmental, behavioral/psychological, and biological (organ system, cellular, and molecular) levels. Centers should propose mechanistic and intervention studies across multiple levels of analysis and across diseases and conditions relevant to the mission of the sponsoring institutes.

The theme of a proposed CPHHD research project may be organized to examine *a*) a single condition for which a significant disparity in morbidity and/or mortality between populations has been demonstrated (e.g., obesity, infant mortality, low birth weight, diabetes, CHD, asthma, cancer), its relationship to multiple social and physical environmental determinants, and their mechanistic pathways; or *b*) a particular category of social environmental determinant (e.g., food supply, urban crowding, built environment, social support) and mechanistic pathways by which it affects multiple health outcomes for which disparities have been demonstrated between populations.

This RFA supports research across multiple levels of analysis. Applicants must develop a thematic focus that can be carried across population(s), behavior, and biologic pathways for the diseases or conditions under study. At least two of the following levels must be addressed in proposed research projects.

Examples of activities relevant to the sponsoring institutes include but are not limited to 1) examining differential social gradients for specific cancer sites and the contribution of known risk factors to these gradients; 2) identifying and elucidating pathways by which the built environment exerts influence on persons with functional disabilities and on diverse health outcomes such as infant morbidity and mortality, asthma, perturbations of the immune system, degenerative or developmental neurologic disorders, cognitive disorders, behavioral disorders, sensory impairment, and cardiovascular disease; 3) elucidating the role of the social and physical environments and behavioral and biologic pathways in explaining the persistent disparities in cervical cancer mortality; 4) evaluating whether social class or other social factors affect the availability and efficacy of therapeutic interventions for diseases such as sickle cell disease that predominately affect specific population subgroups; 5) increasing emphasis on the collection of biomarkers in epidemiologic studies of social relationships and health; 6) examining the consequences of retirement on health and functioning; and 7) characterizing differentials in income and wealth accumulation for subpopulations (such as elderly, racial and ethnic minorities, preretirement workers) and identifying the sources of these differentials and their impacts on health status.

Support of this program will be through the P50 Specialized Centers Grant. The anticipated award date is 1 April 2003.

The sponsoring institutes intend to commit approximately $15 million (NIEHS $5 million, NCI $8 million, and NIA $2 million) in fiscal year 2003 to fund seven or eight new grants in response to this RFA. An applicant may request a project period of up to 5 years and a budget for direct costs of up to $1.3 million per year.

The deadline for receipt of applications is 29 July 2002. Complete information on this RFA is available online at http://grants1.nih.gov/grants/guide/rfa-files/RFA-ES-02-009.html.

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